

## WEST Search History

DATE: Wednesday, April 02, 2003

### Set Name Query

side by side

### Hit Count Set Name

result set

*DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES;  
OP=ADJ*

L10 L9 and anti-HCV adj antibody

39 L10

*DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ*

L9 "ABBOTT LABORAOTRIES" | "ABBOTT LABORATOIRES" |  
"ABBOTT LABORATORIES"

5129 L9

L8 'ABBOTT LABORAOTRIES'!

5129 L8

*DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES;  
OP=ADJ*

L7 Lesniewski R.in.

8 L7

L6 L5 and antibody

2 L6

L5 SCHOFIELD D.in.

15 L5

L4 L3 and envelope adj 2

5 L4

L3 L2 and HCV adj envelope

46 L3

L2 monoclonal adj antibody

55017 L2

L1 HCV adj mono clainal adj antibody

0 L1

END OF SEARCH HISTORY



Entrez	PubMed	Nucleotide	Protein	Genome	Structure	PMC	Journals	B
Search	PubMed	for Houghton M HCV envelope					Preview	Go
<input checked="" type="checkbox"/> Limits		Preview/Index		History		Clipboard		Details

- Search History will be lost after eight hours of inactivity.
- To combine searches use # before search number, e.g., #2 AND #6.
- Search numbers may not be continuous; all searches are represented.

Entrez  
PubMed

Search	Most Recent Queries	Time	Result
#8	Search <b>Houghton M HCV envelope</b> Limits: <b>Publication Date to 1994/07/29</b>	09:38:08	<u>9</u>
#1	Search <b>anti-HCV envelope</b> Field: <b>All Fields</b> , Limits: <b>Publication Date to 1994/07/29</b>	09:36:42	<u>32</u>

PubMed  
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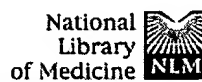
U.S. GOVERNMENT PRINTING OFFICE: 2001-49-034-9

## WEST Search History

DATE: Wednesday, April 02, 2003

<u>Set Name</u> side by side	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u> result set
<i>DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ</i>			
L3	L2 and E2	3	L3
L2	L1 and antibody	26	L2
L1	Houghton M.in.	111	L1

END OF SEARCH HISTORY



PubMed	Nucleotide	Protein	Genome	Structure	PMC	Taxonomy	OMIM	Books
Search	PubMed	for antibody and HCV envelope					Preview	Go
Clear								
<input checked="" type="checkbox"/> Limits   Preview/Index <b>History</b> Clipboard   Details								

- Search History will be lost after one hour of inactivity.
- To combine searches use # before search number, e.g., #2 AND #6.
- Search numbers may not be continuous; all searches are represented.

Entrez  
PubMed

Search	Most Recent Queries	Time	Result
#2	Search <b>antibody and HCV envelope</b> Limits: <b>Publication Date to 1995/07/30</b>	08:03:38	<u>84</u>
#1	Search <b>antibody and HCV</b> Field: <b>All Fields</b> , Limits: <b>Publication Date to 1995/07/30</b>	07:29:11	<u>2794</u>

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Resources

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0

CORPORATE SOURCE: Tomoguri, Tetsushi; Hayasaka, Ikuo  
Department of Pathology, Nihon University School of  
Medicine, Itabashi-ku, Tokyo, 173-8610, Japan  
SOURCE: Vaccine (2002), 20(25-26), 3095-3103  
CODEN: VACCDE; ISSN: 0264-410X  
PUBLISHER: Elsevier Science Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The hypervariable region 1 (HVR1) of hepatitis C virus (HCV) may contain neutralizing epitopes. A chimpanzee in whom cross-reactive anti-HVR1 antibodies had been induced by immunization was challenged with heterologous HCV for clarifying whether cross-reactive anti-HVR1 antibodies can neutralize heterologous HCV. Acute hepatitis C occurred in this chimpanzee after the challenge. Rechallenge with mixts. of the highest titer cross-reactive immune serum and heterologous HCV, after the chimpanzee had cleared the viremia, again resulted in HCV infection. Virus capture assay and inhibition of virus adsorption to susceptible cells, by the immune sera from the chimpanzee and highly cross-reactive **monoclonal antibodies** (mAbs) against the C-terminus of HVR1 of the challenge virus, showed that cross-reactive anti-HVR1 had no cross-neutralizing activity. The data imply that the HVR1 component is insufficient to develop an effective HCV vaccine.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS  
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L9 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2002:555537 CAPLUS  
DOCUMENT NUMBER: 137:124200  
TITLE: Monoclonal antibodies specific to E2 proteins for passive immunotherapy of hepatitis C virus infection  
INVENTOR(S): Fong, Steven K. H.; Hadlock, Kenneth G.; Keck, Zhen-Yong  
PATENT ASSIGNEE(S): Board of Trustees of Leland Stanford Junior University, USA  
SOURCE: PCT Int. Appl., 152 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002057314	A2	20020725	WO 2001-US45029	20011130
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				

PRIORITY APPLN. INFO.: US 2000-728720 A 20001201

AB Conformational epitopes of the **envelope protein E2** of the Hepatitis C virus (HCV) have been identified and characterized using a panel of **monoclonal antibodies** derived from patients infected with HCV. These conformational epitopes have been detd. to be important in the immune response of humans to HCV and may be particularly important in neutralizing the virus. Based on the identification of these conformational epitopes, vaccines contg. peptides and mimotopes with these conformational epitopes intact may be prepd. and administered to patients to prevent and/or treat

HCV infection. The identification of four distinct groups of **monoclonal antibodies** with each directed to a particular epitope of E2 may be used to stratify patients based on their response to HCV and may be used to det. a proper treatment regimen.

L9 ANSWER 5 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:496756 CAPLUS

DOCUMENT NUMBER: 137:123775

TITLE: Structural Features of **Envelope Proteins** on Hepatitis C Virus-like Particles as Determined by Anti-envelope Monoclonal Antibodies and CD81 Binding

AUTHOR(S): Triyatni, Miriam; Vergalla, John; Davis, Anthony R.; Hadlock, Kenneth G.; Fount, Steven K. H.; Liang, T. Jake

CORPORATE SOURCE: Liver Diseases Section, National Institute of Diabetes

and Digestive and Kidney Diseases, NIH, Bethesda, MD, 20892, USA

SOURCE: Virology (2002), 298(1), 124-132

CODEN: VIRLAX; ISSN: 0042-6822

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The envelope glycoprotein E2 of hepatitis C virus (HCV) is a major component of the viral envelope. Knowledge of its topol. features and antigenic determinants in virions is crucial in understanding the viral binding sites to cellular receptor(s) and the induction of neutralizing antibodies. The lack of a robust cell culture system for virus propagation has hampered the characterization of E2 presented on the virion. Here the authors report the structural features of hepatitis C virus-like particles (HCV-LPs) of the 1a and 1b genotypes as detd. by various mouse and human monoclonal anti-envelope antibodies.

Our results show that the E2 protein of HCV-LPs reacts with human **monoclonal antibodies** recognizing conformational determinants. **Monoclonal antibodies** (mAbs) specific for the hypervariable region 1 (HVR-1) sequence reacted strongly with HCV-LPs, suggesting that the HVR-1 is exposed on the viral surface. Several mAbs recognized both HCV-LPs with equally high affinity, indicating that the corresponding epitopes [amino acids (aa) 192-217 of E1 and aa 412-423, aa 522-531, and aa 640-653 of E2] are conserved in both genotypes and exposed on the surface of the HCV-LP. The E2 and E1/E2 dimers of 1a bound strongly to the recombinant large extracellular loop (LEL) of CD81 (CD81-LEL) of human and African green monkey, while the HCV-LP of 1a bound weakly to human CD81-LEL. E1/E2 dimers and the HCV-LPs of 1b did not bind CD81-LEL, consistent with the notion that CD81 recognition by E2 is strain-specific and does not correlate with permissiveness of infection. A model of the topol. and exposed antigenic determinants of the **envelope proteins** of HCV is proposed.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 6 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:471385 CAPLUS

DOCUMENT NUMBER: 137:197234

TITLE: Reconstitution of hepatitis C virus envelope glycoproteins into liposomes as a surrogate model to study virus attachment

AUTHOR(S): Lambot, Michel; Fretier, Stephanie; Op De Beeck, Anne;

CORPORATE SOURCE: Quatannens, Brigitte; Lestavel, Sophie; Clavey, Veronique; Dubuisson, Jean

SOURCE: CNRS-Institut de Biologie de Lille and Institut Pasteur de Lille, Lille, 59021, Fr.

PUBLISHER: Journal of Biological Chemistry (2002), 277(23), 20625-20630

DOCUMENT TYPE: CODEN: JBCHA3; ISSN: 0021-9258

LANGUAGE: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The envelope glycoproteins, E1 and E2, of hepatitis C virus (HCV) assemble intracellularly to form a noncovalent heterodimer that is expected to be essential for viral assembly and entry. However, due to the lack of a cell culture system supporting efficient HCV replication, it is very difficult to obtain relevant information on the functions of this glycoprotein oligomer. To get better insights into its biol. and biochem. properties, HCV envelope glycoprotein heterodimer expressed by a vaccinia virus recombinant was purified by immunoaffinity. Purified E1E2 heterodimer was recognized by conformation-dependent **monoclonal antibodies**, showing that the proteins were properly folded. In addn., it interacted with human CD81, a putative HCV receptor, as well as with human low and very low d. lipoproteins, which have been shown to be assocd. with infectious HCV particles isolated from patients. Purified E1E2 heterodimer was also reconstituted into liposomes. E1E2-liposomes were recognized by a conformation-dependent **monoclonal antibody** as well as by human CD81. Together, these data indicate that E1E2-liposomes are a valuable tool to study the mol. requirements for HCV binding to target cells.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L9 ANSWER 7 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:180436 CAPLUS

DOCUMENT NUMBER: 137:227162

TITLE: Cloning and expression of human CD81 major extracellular loop in E. coli and its activity

AUTHOR(S): Zhang, Guojun; Ling, Shigan; Song, Xiaoguo; Zhang, Heqiu; Chen, Kun; Zhu, Cuixia; Xiu, Bingshui

CORPORATE SOURCE: Institute of Basic Medical Sciences, Academy of Military Medical Sciences, Beijing, 100850, Peop. Rep.

SOURCE: China

PUBLISHER: Junshi Yixue Kexueyuan Yuankan (2001), 25(4), 260-264

DOCUMENT TYPE: CODEN: JYKYEL; ISSN: 1000-5501

LANGUAGE: Chinese

AB An expression plasmid for a fusion protein of human CD81 major extracellular loop was constructed and binding activity of its expressed protein with HCV E2 was studied. CD81 major extracellular loop

sequence was amplified from human peripheral blood lymphocytes by RT-PCR, then inserted into the expression vector pBVIL1, and expressed in E. coli.

The purified fusion protein was tested for binding activity with E2. CD81-EC2 gene was correctly amplified and inserted into the vector as confirmed by sequencing. The preliminary study showed that the recombinant CD81/EC2 could bind truncated HCV E2 (384-661) protein expressed in E. coli. This work proved the way for further study on interactions of CD81 with HCV and its E2, and for prepn. of anti-EC2 monoclonal antibody.

L9 ANSWER 8 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:90110 CAPLUS

DOCUMENT NUMBER: 136:149867

TITLE: Human monoclonal antibody against hepatitis c virus E2

glycoprotein  
INVENTOR(S): Kubanek, Bernhard; Cardoso, Marcia Da Silva; Siemoneit, Karl; Dagan, Shlomo; Eren, Rachel  
PATENT ASSIGNEE(S): DRK-Blutspendedienst Baden-Wurttemberg, Germany  
SOURCE: PCT Int. Appl., 31 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent  
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008292	A2	20020131	WO 2001-IL684	20010725
WO 2002008292	A3	20021212		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IL 2000-137522 A 20000726

AB Disclosed is a hybridoma cell line which produces human antibodies capable

of binding to the hepatitis C virus (HCV) E2 glycoprotein and capable of neutralizing HCV infection in vivo in an animal model, as well as antibodies produced by the cell line. Also disclosed are various uses of said antibodies in the prevention and treatment of HCV infection. Peripheral blood lymphocytes obtained from human donors having a high titer of anti HCV E2 antibodies are transformed in vitro by Epstein-Barr virus and then fused with heteromyeloma cells to generate hybridomas secreting human antibodies having a high affinity and specificity to HCV E2 glycoprotein.

L9 ANSWER 9 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:79471 CAPLUS

DOCUMENT NUMBER: 136:260957

TITLE: Binding of hepatitis C virus-like particles derived from infectious clone H77C to defined human cell

lines

AUTHOR(S): Wellnitz, Sabine; Klumpp, Bettina; Barth, Heidi; Ito,

Susumu; Depla, Erik; Dubuisson, Jean; Blum, Hubert  
E.;

Baumert, Thomas F.  
CORPORATE SOURCE: Department of Medicine II, University of Freiburg,  
Freiburg, D-79106, Germany

SOURCE: Journal of Virology (2002), 76(3), 1181-1193  
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hepatitis C virus (HCV) is a leading cause of chronic hepatitis  
in the world. The study of viral entry and infection has been hampered  
by

the inability to efficiently propagate the virus in cultured cells and  
the

lack of a small-animal model. Recent studies have shown that in insect  
cells, the HCV structural proteins assemble into HCV  
-like particles (HCV-LPs) with morphol., biophys., and antigenic  
properties similar to those of putative virions isolated from HCV  
-infected humans. In this study, we used HCV-LPs derived from  
infectious clone H77C as a tool to examine virus-cell interactions. The  
binding of partially purified particles to human cell lines was analyzed  
by fluorescence-activated cell sorting with defined monoclonal  
antibodies to envelope glycoprotein E2. HCV-LPs  
demonstrated dose-dependent and saturable binding to defined human  
lymphoma and hepatoma cell lines but not to mouse cell lines. Binding  
could be inhibited by monoclonal anti-E2 antibodies, indicating that the  
HCV-LP-cell interaction was mediated by envelope glycoprotein E2.  
Binding appeared to be CD81 independent and did not correlate with low-d.  
lipoprotein receptor expression. Heat denaturation of HCV-LPs  
drastically reduced binding, indicating that the interaction of  
HCV-LPs with target cells was dependent on the proper conformation  
of the particles. In conclusion, our data demonstrate that insect  
cell-derived HCV-LPs bind specifically to defined human cell  
lines. Since the envelope proteins of HCV  
-LPs are presumably presented in a virion-like conformation, the binding  
of HCV-LPs to target cells may allow the study of virus-host  
cell interactions, including the isolation of HCV receptor  
candidates and antibody-mediated neutralization of binding.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR  
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RECORD. ALL CITATIONS AVAILABLE IN THE RE  
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L9 ANSWER 10 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:37700 CAPLUS

DOCUMENT NUMBER: 136:231146

TITLE: Binding of the hepatitis C virus envelope  
protein E2 to CD81 inhibits natural killer  
cell functions

AUTHOR(S): Tseng, Chien-Te K.; Klimpel, Gary R.

CORPORATE SOURCE: Department of Microbiology and Immunology, University  
of Texas Medical Branch, Galveston, TX, 77555, USA

SOURCE: Journal of Experimental Medicine (2002), 195(1),  
43-49

CODEN: JEMEAV; ISSN: 0022-1007

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Infection with hepatitis C virus (HCV) is a leading cause of

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NEWS 4 Apr 09 ZDB will be removed from STN  
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IFIUDB  
NEWS 6 Apr 22 Records from IP.com available in CAPLUS, HCAPLUS, and  
ZCAPLUS  
NEWS 7 Apr 22 BIOSIS Gene Names now available in TOXCENTER  
NEWS 8 Apr 22 Federal Research in Progress (FEDRIP) now available  
NEWS 9 Jun 03 New e-mail delivery for search results now available  
NEWS 10 Jun 10 MEDLINE Reload  
NEWS 11 Jun 10 PCTFULL has been reloaded  
NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment  
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saved answer sets no longer valid  
NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY  
NEWS 15 Jul 30 NETFIRST to be removed from STN  
NEWS 16 Aug 08 CANCERLIT reload  
NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN  
NEWS 18 Aug 08 NTIS has been reloaded and enhanced  
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now available on STN  
NEWS 20 Aug 19 IFIPAT, IFICDB, and IFIUDB have been reloaded  
NEWS 21 Aug 19 The MEDLINE file segment of TOXCENTER has been reloaded  
NEWS 22 Aug 26 Sequence searching in REGISTRY enhanced  
NEWS 23 Sep 03 JAPIO has been reloaded and enhanced  
NEWS 24 Sep 16 Experimental properties added to the REGISTRY file  
NEWS 25 Sep 16 CA Section Thesaurus available in CAPLUS and CA  
NEWS 26 Oct 01 CASREACT Enriched with Reactions from 1907 to 1985  
NEWS 27 Oct 21 EVENTLINE has been reloaded  
NEWS 28 Oct 24 BEILSTEIN adds new search fields  
NEWS 29 Oct 24 Nutraceuticals International (NUTRACEUT) now available on  
STN  
NEWS 30 Oct 25 MEDLINE SDI run of October 8, 2002  
NEWS 31 Nov 18 DKILIT has been renamed APOLLIT  
NEWS 32 Nov 25 More calculated properties added to REGISTRY  
NEWS 33 Dec 02 TIBKAT will be removed from STN  
NEWS 34 Dec 04 CSA files on STN  
NEWS 35 Dec 17 PCTFULL now covers WP/PCT Applications from 1978 to date  
NEWS 36 Dec 17 TOXCENTER enhanced with additional content  
NEWS 37 Dec 17 Adis Clinical Trials Insight now available on STN  
NEWS 38 Dec 30 ISMEC no longer available  
NEWS 39 Jan 21 NUTRACEUT offering one free connect hour in February 2003  
NEWS 40 Jan 21 PHARMAML offering one free connect hour in February 2003  
NEWS 41 Jan 29 Simultaneous left and right truncation added to COMPENDEX,  
ENERGY, INSPEC

NEWS 42 Feb 13 CANCERLIT is no longer being updated  
 NEWS 43 Feb 24 METADEX enhancements  
 NEWS 44 Feb 24 PCTGEN now available on STN  
 NEWS 45 Feb 24 TEMA now available on STN  
 NEWS 46 Feb 26 NTIS now allows simultaneous left and right truncation  
 NEWS 47 Feb 26 PCTFULL now contains images  
 NEWS 48 Mar 04 SDI PACKAGE for monthly delivery of multifile SDI results  
 NEWS 49 Mar 19 APOLLIT offering free connect time in April 2003  
 NEWS 50 Mar 20 EVENTLINE will be removed from STN  
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 NEWS 53 Mar 24 Indexing from 1957 to 1966 added to records in CA/CAPLUS

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 CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),  
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FILE COVERS 1907 - 2 Apr 2003 VOL 138 ISS 14  
FILE LAST UPDATED: 1 Apr 2003 (20030401/ED)

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

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    268386 "ANTIBODIES"
    370923 "ANTIBODY"
        ("ANTIBODY" OR "ANTIBODIES")
    0 "15C8C1"
L1    0 "ANTIBODY 15C8C1"
        ("ANTIBODY" (W) "15C8C1")
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    268386 "ANTIBODIES"
    370923 "ANTIBODY"
        ("ANTIBODY" OR "ANTIBODIES")
    0 "12D11F1"
L2    0 "ANTIBODY 12D11F1"
        ("ANTIBODY" (W) "12D11F1")
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=> "8G10D1H9"
L3    0 "8G10D1H9"
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    268386 "ANTIBODIES"
    370923 "ANTIBODY"
        ("ANTIBODY" OR "ANTIBODIES")
    0 "9G3E6"
L4    0 "ANTIBODY 9G3E6"
        ("ANTIBODY" (W) "9G3E6")
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=> "antibody10D3C4"
L5    0 "ANTIBODY10D3C4"
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=> "antibody 4H6B2"
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    268386 "ANTIBODIES"
    370923 "ANTIBODY"
        ("ANTIBODY" OR "ANTIBODIES")
    0 "4H6B2"
L6    0 "ANTIBODY 4H6B2"
        ("ANTIBODY" (W) "4H6B2")
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=> "antibody 17F2C2"
    244443 "ANTIBODY"
    268386 "ANTIBODIES"
    370923 "ANTIBODY"
        ("ANTIBODY" OR "ANTIBODIES")
    0 "17F2C2"
L7    0 "ANTIBODY 17F2C2"
        ("ANTIBODY" (W) "17F2C2")
```

```
=> HCV (1) monoclonal (w) antibody
    6301 HCV
```

15 HCVS  
 6304 HCV  
 (HCV OR HCVS)  
 117813 MONOCLONAL  
 494 MONOCLONALS  
 117871 MONOCLONAL  
 (MONOCLONAL OR MONOCLONALS)  
 244443 ANTIBODY  
 268386 ANTIBODIES  
 370923 ANTIBODY  
 (ANTIBODY OR ANTIBODIES)  
 L8 190 HCV (L) MONOCLONAL (W) ANTIBODY

=> envelope (w) protein and L8  
 43704 ENVELOPE  
 8153 ENVELOPES  
 48477 ENVELOPE  
 (ENVELOPE OR ENVELOPES)  
 1495376 PROTEIN  
 1007354 PROTEINS  
 1728522 PROTEIN  
 (PROTEIN OR PROTEINS)  
 8890 ENVELOPE (W) PROTEIN  
 L9 30 ENVELOPE (W) PROTEIN AND L8

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L9 ANSWER 1 OF 30 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:198871 CAPLUS  
 TITLE: Infectious hepatitis C virus pseudo-particles  
 containing functional E1-E2 **envelope**  
**protein** complexes  
 AUTHOR(S): Bartosch, Birke; Dubuisson, Jean; Cosset,  
 Francois-Loic  
 CORPORATE SOURCE: Laboratoire de Vectorologie Retrovirale et Therapie  
 Genique, Institut National de la Sante et de la  
 Recherche Medicale U412, IFR 128, Ecole Normale  
 Supérieure de Lyon, Lyon, 69364/07, Fr.  
 SOURCE: Journal of Experimental Medicine (2003), 197(5),  
 633-642  
 CODEN: JEMEAV; ISSN: 0022-1007  
 PUBLISHER: Rockefeller University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The study of hepatitis C virus (HCV), a major cause of chronic  
 liver disease, has been hampered by the lack of a cell culture system  
 supporting its replication. Here, we have successfully generated  
 infectious pseudo-particles that were assembled by displaying unmodified  
 and functional HCV glycoproteins onto retroviral and lentiviral  
 core particles. The presence of a green fluorescent protein marker gene  
 packaged within these HCV pseudo-particles allowed reliable and  
 fast detn. of infectivity mediated by the HCV glycoproteins.  
 Primary hepatocytes as well as hepato-carcinoma cells were found to be  
 the major targets of infection in vitro. High infectivity of the  
 pseudo-particles required both E1 and E2 HCV glycoproteins, and  
 was neutralized by sera from HCV-infected patients and by some

anti-E2 **monoclonal antibodies**. In addn., these pseudo-particles allowed investigation of the role of putative **HCV** receptors. Although our results tend to confirm their involvement, they provide evidence that neither LDLr nor CD81 is sufficient to mediate **HCV** cell entry. Altogether, these studies indicate that these pseudo-particles may mimic the early infection steps of parental **HCV** and will be suitable for the development of much needed new antiviral therapies.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 2 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:23978 CAPLUS

DOCUMENT NUMBER: 138:104796

TITLE: Recognition of native hepatitis C virus E1E2 heterodimers by a human monoclonal antibody

AUTHOR(S): Cocquerel, Laurence; Quinn, Elizabeth R.; Flint, Mike;

Hadlock, Kenneth G.; Fount, Steven K. H.; Levy, Shoshana

CORPORATE SOURCE: Departments of Medicine/Division of Oncology, Stanford

SOURCE: University Medical Center, Stanford, CA, 94305, USA  
Journal of Virology (2003), 77(2), 1604-1609

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The majority of hepatitis C virus (**HCV**)-infected individuals progress from acute to chronic disease; despite the presence of a strong humoral immune response to the envelope glycoproteins E1 and E2. When expressed in mammalian cells, E1 and E2 form both noncovalently linked E1E2 heterodimers, believed to be properly folded, and disulfide-linked, high-mol.-wt. aggregates that are misfolded. Previously, we identified

10

human **monoclonal antibodies** (HMABs) that bind E2 glycoproteins from different genotypes. Here we demonstrate that one of these HMABs, CBH-2, is unique in its ability to distinguish between properly folded and misfolded **envelope proteins**. This HMAB recognizes **HCV**-E2 only when complexed with E1. The E1E2 complexes recognized by CBH-2 are noncovalently linked heterodimers and not misfolded disulfide-linked, high-mol.-wt. aggregates. The E1E2 heterodimers seen by CBH-2 no longer assoc. with the endoplasmic reticulum chaperone calnexin and are likely to represent the prebudding form of the **HCV** virion.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:600860 CAPLUS

DOCUMENT NUMBER: 138:71506

TITLE: In vivo and in vitro evidence that cross-reactive antibodies to C-terminus of hypervariable region 1 do not neutralize heterologous hepatitis C virus

AUTHOR(S): Esumi, Mariko; Zhou, Yi-Hua; Tanoue, Tetsuya;

chronic liver disease worldwide. Little is known about how this virus is able to persist or whether this persistence might be because of its ability to alter the early innate immune response. The major **HCV envelope protein** E2 has been shown to bind to CD81.

Thus, **HCV** binding to natural killer (NK) cells could result in the crosslinking of CD81. To explore this possibility, we investigated whether crosslinking CD81 on NK cells could alter NK cell function. CD81 crosslinking by **monoclonal antibody** (mAb) specific for CD81 or by immobilized E2 have been shown to result in costimulatory signals for human T cells. In this study, we show that CD81 crosslinking via immobilized E2 or mAbs specific for CD81 inhibits not only non major histocompatibility complex-restricted cytotoxicity mediated by NK cells but also interferon (IFN)-.gamma. prodn. by NK cells after exposure to interleukin (IL)-2, IL-12, IL-15, or CD16 crosslinking. These results show that CD81 crosslinking mediates completely different signals in NK cells vs. T cells. Importantly, these results suggest that one mechanism whereby **HCV** can alter host defenses and innate immunity is via-the early inhibition of IFN-.gamma. prodn. by NK cells.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 11 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:912910 CAPLUS

DOCUMENT NUMBER: 137:104371

TITLE: Secretory expression of different C-terminal truncated

AUTHOR(S): HCV E1 proteins in mammalian cells and characterization of the expressed products  
Zhu, Jun; Kong, Yuying; Liu, Jing; Zhang, Zuchuan; Wang, Yuan; Li, Guangdi  
CORPORATE SOURCE: Institute of Biochemistry and Cell Biology, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China  
SOURCE: Shengwu Huaxue Yu Shengwu Wuli Xuebao (2001), 33(6), 634-640  
CODEN: SHWPAU; ISSN: 0582-9879  
PUBLISHER: Shanghai Kexue Jishu Chubanshe  
DOCUMENT TYPE: Journal  
LANGUAGE: Chinese

AB Three fragments of **HCV** envelope 1 (E1) with different C-terminal truncation at aa310, aa325, aa340 were cloned into the mammalian expression vector pSecTagB. An epitope in the hepatitis B surface antigen, preS1(21-47), were genetically engineered onto the N-terminus of the recombinant protein and used as an affinity tag for detection and purifn. The resulting pSec-preS1-E1t310, pSec-preS1-E1t325, and pSec-preS1-E1t340 were transiently expressed in the HeLa cells and antigenicity, secretory efficiency, and glycosylation type of the recombinant E1 proteins were compared. All of the three recombinant proteins could be detected by both preS1 **monoclonal antibody** and E1 polyclonal antiserum. The expression products were secreted and highly mannose-type glycosylated, with S1E1t325 being secreted, indicating the influence of the hydrophobic regions on the secretion of the E1 protein. Three CHO cell lines expressing the proteins, S1E1t310, S1E1t325, and S1E1t340, were established and CHO/pSecS1E1t325 was chosen for further study. The secreted S1E1t325 could be enriched from cell culture medium by the preS1 antibody-coupled Sepharose. The glycosylation anal. indicated the lack of complex glycogen

even after the E1 was secreted via Golgi complexes. The established stable cell lines and anti-preS1 affinity method could be utilized to enrich and purify the HCV E1 expressed in mammalian cells, and may be used for further characterization of this protein.

L9 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:888373 CAPLUS

DOCUMENT NUMBER: 136:133315

TITLE: Production and characterization of monoclonal antibodies specific for a conserved epitope within hepatitis C virus hypervariable region 1

AUTHOR(S): Li, Chengyao; Candotti, Daniel; Allain, Jean-Pierre

CORPORATE SOURCE: Division of Transfusion Medicine, East Anglia Blood Centre, National Blood Service, Cambridge, CB2 2PT, UK

SOURCE: Journal of Virology (2001), 75(24), 12412-12420  
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Frequent mutations in hypervariable region 1 (HVR1) of the main envelope protein of hepatitis C virus (HCV) is a major mechanism of persistence by escaping the host immune recognition. HVR1 contains an epitope eliciting neutralizing antibodies. This study was aimed to prep. broadly cross-reacting, high-affinity, monoclonal antibodies (MAb) to the HVR1 C terminus of HCV with potential therapeutic neutralizing capacity. A conserved amino residue group of glycine (G) at position 23 and glutamic acid (Q)

at position 26 in HVR1 was confirmed as a key epitope against which two MAbs were selected and characterized. MAbs 2P24 and 15H4 were IgG1 kappa chain

[IgG1(.kappa.)], cross-reacted with 32 and 30 of 39 random C-terminal HVR1

peptides, resp., and did not react with other HCV peptides. The VH of 2P24 and 15H4 heavy chains originated from Igh germ line V gene family 1 and 8, resp. In contrast, the VL .kappa. sequences were highly homologous. The affinity (Kd) of 2P24 and 15H4 (10<sup>-9</sup> or 10<sup>-8</sup> M with two immunizing peptides and 10<sup>-8</sup> M with two non-immunizing HVR1 peptides) paralleled the reactivity obtained with peptide enzyme immunoassay. MAbs 2P24 and 15H4 captured 25 of 31 (81%) HCV in unselected patients' plasmas. These antibodies also blocked HCV binding to Molt-4 cells in a dose-dependent fashion. The data presented suggest that

broadly cross-reactive MAbs to a conserved epitope within HCV HVR1 can be produced. Clin. application for passive immunization in HCV-related chronic liver disease and after liver transplantation is considered.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS

FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L9 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:543686 CAPLUS

DOCUMENT NUMBER: 135:255709

TITLE: Fluorescence correlation spectroscopy as a method for assessment of interactions between phage displaying antibodies and soluble antigen

AUTHOR(S): Lagerkvist, Ann Catrin; Foldes-Papp, Zeno; Persson,

CORPORATE SOURCE: Mats A. A.; Rigler, Rudolf  
Karolinska Institutet, Department of Medicine and  
Center for Molecular Medicine (L8:01), Karolinska  
Hospital, Stockholm, S-171 76, Swed.  
SOURCE: Protein Science (2001), 10(8), 1522-1528  
CODEN: PRCIEI; ISSN: 0961-8368  
PUBLISHER: Cold Spring Harbor Laboratory Press  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Phage display is widely used for expression of combinatorial libraries, not least for protein engineering purposes. Precise selection at the single mol. level will provide an improved tool for generating proteins with complex and distinct properties from large mol. libraries. To establish such an improved selection system, the authors here report the detection of specific interactions between phage with displayed antibody fragments and fluorescently labeled sol. antigen based on Fluorescence Correlation Spectroscopy (FCS). Our novel strategy comprises the use of two sep. fluorochromes for detection of the phage-antigen complex, either with labeled anti-phage antibody or using a labeled antigen. As a model system, the authors studied a human **monoclonal antibody** to the hepatitis-C virus (**HCV**) **envelope protein** E2 and its cognate antigen (rE2 or rE1/E2). The authors could thus assess the specific interactions and det. the fraction of specific vs. background phage (26% specific phage). Aggregation of these particular antigens made it difficult to reliably utilize the full potential of cross-correlation studies using the two labels simultaneously. However, with true monomeric proteins, this will certainly be possible, offering a great advantage in a safer and highly specific detection system.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 14 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:799830 CAPLUS  
DOCUMENT NUMBER: 134:70078  
TITLE: Human monoclonal antibodies that inhibit binding of hepatitis C virus E2 protein to CD81 and recognize conserved conformational epitopes  
AUTHOR(S): Hadlock, Kenneth G.; Lanford, Robert E.; Perkins, Susan; Rowe, Judy; Yang, Qing; Levy, Shoshana; Pileri,

Piero; Abrignani, Sergio; Fount, Steven K. H.  
CORPORATE SOURCE: Department of Pathology, Stanford University, Stanford, CA, USA  
SOURCE: Journal of Virology (2000), 74(22), 10407-10416  
CODEN: JOVIAM; ISSN: 0022-538X  
PUBLISHER: American Society for Microbiology  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The intrinsic variability of hepatitis C virus (**HCV**) **envelope proteins** E1 and E2 complicates the identification of protective antibodies. In an attempt to identify antibodies to E2 proteins from divergent **HCV** isolates, we produced **HCV** E2 recombinant proteins from individuals infected with **HCV** genotypes 1a, 1b, 2a, and 2b. These proteins were then used to characterize 10 human **monoclonal antibodies** (HMABs) produced from peripheral B cells isolated from an individual infected with **HCV** genotype 1b. Nine of the antibodies recognize

conformational epitopes within **HCV** E2. Six HMABs identify epitopes shared among **HCV** genotypes 1a, 1b, 2a, and 2b. Six, including five broadly reactive HMABs, could inhibit binding of **HCV** E2 of genotypes 1a, 1b, 2a, and 2b to human CD81 when E2 and the antibody were simultaneously exposed to CD81. Surprisingly, all of the antibodies that inhibited the binding of E2 to CD81 retained the ability to recognize preformed CD81-E2 complexes generated with some of the same recombinant E2 proteins. Two antibodies that did not recognize preformed complexes of **HCV** 1a E2 and CD81 also inhibited binding of **HCV** 1a virions to CD81. Thus, **HCV**-infected individuals can produce antibodies that recognize conserved conformational epitopes and inhibit the binding of **HCV** to CD81. The inhibition is mediated via antibody binding to epitopes outside of the CD81 binding site in E2, possibly by preventing conformational changes in E2 that are required for CD81 binding.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L9 ANSWER 15 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:729204 CAPLUS

DOCUMENT NUMBER: 134:3841

TITLE: Recombinant human monoclonal antibodies against different conformational epitopes of the E2 envelope glycoprotein of hepatitis C virus that inhibit its interaction with CD81

AUTHOR(S): Allander, Tobias; Drakenberg, Katarina; Beyene, Aster;

Rosa, Domenico; Abrignani, Sergio; Houghton, Michael; Widell, Anders; Grillner, Lena; Persson, Mats A. A. CORPORATE SOURCE: Karolinska Institute, Department of Medicine and Department of Laboratory Medicine, Center for Molecular Medicine (L8:01), Karolinska Hospital, Stockholm, S-171 76, Swed.

SOURCE: Journal of General Virology (2000), 81(10), 2451-2459  
CODEN: JGVIAY; ISSN: 0022-1317

PUBLISHER: Society for General Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The antibody response to the **envelope proteins** of hepatitis C virus (**HCV**) may play an important role in controlling the infection. To allow mol. analyses of protective antibodies, we isolated human **monoclonal antibodies** to the E2 envelope glycoprotein of **HCV** from a combinatorial Fab library established from bone marrow of a chronically **HCV**-infected patient. Anti-E2 reactive clones were selected using recombinant E2 protein. The bone marrow donor carried **HCV** genotype 2b, and E2 used for selection was of genotype 1a. The antibody clones were expressed as Fab fragments in *E. coli*, and as Fab fragments and IgG1 in CHO cells. Seven different antibody clones were characterized, and shown to have high affinity for E2, genotype 1a.

Three

clones also had high affinity for E2 of genotype 1b. They all bind to conformation-dependent epitopes. Five clones compete for the same or overlapping binding sites, while two bind to one or two other epitopes of E2. Four clones corresponding to the different epitopes were tested as purified IgG1 for blocking the CD81-E2 interaction in vitro; all four were

pos. at 0.3-0.5 .mu.g/mL. Thus, the present results suggest the existence of at least two conserved epitopes in E2 that mediate inhibition of the E2-CD81 interaction, of which one appeared immunodominant in this donor.  
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L9 ANSWER 16 OF 30 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2000:577492 CAPLUS  
DOCUMENT NUMBER: 133:134178  
TITLE: Monoclonal antibodies against hepatitis C virus nonstructural protein 4 and hybridomas  
INVENTOR(S): Li, Defu; Yin, Hongzhang; Li, Xiuhua; Meng, Shuhua; Liu, Ying; Zhang, Ning  
PATENT ASSIGNEE(S): China Medicine & Biological Product Inspection Center,  
Peop. Rep. China  
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 24 pp.  
CODEN: CNXXEV  
DOCUMENT TYPE: Patent  
LANGUAGE: Chinese  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1230591	A	19991006	CN 1998-117114	19980731
CN 1089802	B	20020828		

PRIORITY APPLN. INFO.: CN 1998-117114 19980731  
AB Anti-HCV core antigen, anti-HCV envelope antigen, anti-HCV NS3 protein, anti-HCV NS4 protein, and anti-HCV NS5 protein **monoclonal antibodies** are raised by immunizing Balb/c mice with resp. antigenic peptide. Five hybridoma cell lines capable of producing the **monoclonal antibodies** specific for HCV core antigen, envelope antigen, NS3 protein, NS4 protein, and NS5 protein are prepd. by conventional hybridoma technol. The five **monoclonal antibodies** were purified, labeled with horse radish peroxidase, are used for detection of HCV antigen in blood products for transfusion and diagnosis and treatment of HCV infection.

L9 ANSWER 17 OF 30 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2000:314876 CAPLUS  
DOCUMENT NUMBER: 132:331678  
TITLE: Human Pan-HCV human **monoclonal antibodies** binding to epitopes of E2 proteins and application for diagnosis and therapy of hepatitis  
C  
INVENTOR(S): Fount, Steven K. H.; Hadlock, Kenneth G.  
PATENT ASSIGNEE(S): The Board of Trustees of Leland Stanford Junior University, USA  
SOURCE: PCT Int. Appl., 85 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000026418	A1	20000511	WO 1999-US25711	19991029
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1127170	A1	20010829	EP 1999-971468	19991029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002528140	T2	20020903	JP 2000-579790	19991029
PRIORITY APPLN. INFO.: US 1998-187057 A 19981105 WO 1999-US25711 W 19991029				
AB Human <b>monoclonal antibodies</b> binding to epitopes common to type 1 and 2 <b>HCV</b> are provided, as well as conformationally conserved <b>HCV</b> E2 2a and 2b proteins. Compns. comprising the antibodies find use in diagnosis and therapy. The antibodies recognize conformational epitopes that are conserved across multiple genotypes of <b>HCV</b> . Thus the antibodies have the potential to be useful in the prevention and treatment of the majority of <b>HCV</b> infections. A subset of the antibodies (CBH-2, CBH-5, CBH-7, CBH-8C, CBH-8E, and CBH-11) have the ability to prevent the binding of <b>HCV</b> E2 proteins of multiple genotypes to human CD81, a possible coreceptor for <b>HCV</b> infection. A subset of the antibodies (CBH-2 and CBH-5) have been shown to inhibit the binding of <b>HCV</b> virions (as opposed to purified E2 protein) to human CD81. A further subset of the antibodies (CBH-4D, CBH-4B, CBH-8C, and CBH-9) have been shown to prevent <b>HCV</b> envelope mediated fusion using an <b>HCV</b> pseudotype system.				
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE				
FORMAT				
L9 ANSWER 18 OF 30 CAPLUS COPYRIGHT 2003 ACS ACCESSION NUMBER: 1999:811351 CAPLUS DOCUMENT NUMBER: 132:45823 TITLE: Methods of presenting antigenic regions of hepatitis C virus <b>envelope protein</b> on cell surfaces for vaccine and immunodiagnostic use INVENTOR(S): Forns, Xavier; Emerson, Suzanne U.; Bukh, Jens; Purcell, Robert H. PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA SOURCE: PCT Int. Appl., 50 pp. CODEN: PIXXD2 DOCUMENT TYPE: Patent LANGUAGE: English FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:				

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966033	A1	19991223	WO 1999-US12665	19990604
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,				

DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,  
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,  
MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,  
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,  
MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,  
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9943350 A1 20000105 AU 1999-43350 19990604  
PRIORITY APPLN. INFO.: US 1998-89779P P 19980618  
WO 1999-US12665 W 19990604

AB A method of increasing the antigenicity of the E1 and E2 envelope glycoproteins of hepatitis C virus by incorporating them into the plasma membrane and presenting them on cell surfaces is described. Host cells presenting a truncated form of the **envelope protein** on their cell surface are disclosed as useful as antigens in diagnostic assays to detect the presence of anti-HCV antibodies, as a panning agent for screening combinatorial libraries to identify **monoclonal antibodies** specific for HCV **envelope protein(s)**, and as a tissue culture system for generating pseudovirions useful for identifying antibodies which exhibit neutralizing activity. The protein is directed to the cell surface using an endoplasmic reticulum signal peptide and is retained in the membrane using a plasma membrane anchor peptide. Use of the transmembrane domain of a PDGF receptor as the anchor domain is demonstrated. When the E2 protein of the H77 strain of HCV was synthesized without a signal peptide or transmembrane domain, the protein was accumulated in the cytosol. A fusion protein of 384-715-glycoprotein E2 and the PDGF receptor was found on the cell surface. Mice injected with the expression vector for the fusion protein showed development of antibodies to E2. The efficiency of the response was dependent on the route of delivery: 2 of 5 mice injected i.m. mounted a response, whereas all the animals inoculated intraepidermally with a gene gun showed an early, strong immune response. Epitope mapping suggested that most of the epitopes of the E2 glycoprotein are conformational rather than linear.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 19 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:640560 CAPLUS

DOCUMENT NUMBER: 131:270949

TITLE: Epitopes in viral **envelope proteins** and specific antibodies directed against these epitopes: use for detection of HCV viral antigen in host tissue

PATENT ASSIGNEE(S): Innogenetics N.V., Belg.

SOURCE: Eur. Pat. Appl., 32 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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EP 947525 A1 19991006 EP 1998-870060 19980327  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO  
CA 2321179 AA 19991007 CA 1999-2321179 19990329  
WO 9950301 A2 19991007 WO 1999-EP2154 19990329  
WO 9950301 A3 19991125  
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,  
DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,  
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,  
MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,  
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,  
MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,  
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
AU 9936022 A1 19991018 AU 1999-36022 19990329  
BR 9909026 A 20001205 BR 1999-9026 19990329  
EP 1064309 A2 20010103 EP 1999-917909 19990329  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO  
JP 2002510038 T2 20020402 JP 2000-541203 19990329  
NZ 506553 A 20021126 NZ 1999-506553 19990329  
US 6521403 B1 20030218 US 2000-645470 20000824  
PRIORITY APPLN. INFO.: EP 1998-870060 A 19980327  
WO 1999-EP2154 W 19990329

AB Antibodies to two new epitopes on the **HCV envelope proteins** were identified which allow routine detection of native **HCV** envelope antigens, in tissue or cells derived from the host. The new epitopes are: the E1 region aa 307-326 and the N-terminal hyper variable region of E2 aa 395-415. Surprisingly, we characterized an antibody which reacts with various sequences of the hypervariable domain of E2. Specific **monoclonal antibodies** directed against these epitopes and allowing routine detection of viral antigen are

described.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 20 OF 30 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 1999:298250 CAPLUS  
DOCUMENT NUMBER: 131:127333  
TITLE: Use of a novel hepatitis C virus (HCV) major-epitope chimeric polypeptide for diagnosis of HCV infection  
AUTHOR(S): Chien, David Y.; Arcangel, Phillip; Medina-Selby, Angelica; Coit, Doris; Baumeister, Mark; Nguyen, Steve; George-Nascimento, Carlos; Gyenes, Alexander; Kuo, George; Valenzuela, Pablo  
CORPORATE SOURCE: Chiron Corporation, Emeryville, CA, 94507, USA  
SOURCE: Journal of Clinical Microbiology (1999), 37(5), 1393-1397  
CODEN: JCMIDW; ISSN: 0095-1137  
PUBLISHER: American Society for Microbiology  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The genome of hepatitis C virus (**HCV**) consists of seven functional regions: the core, E1, E2/NS1, NS2, NS3, NS4, and NS5 regions. The U.S. Food and Drug Administration-licensed 2.0G immunoassay for the detection of anti-**HCV** uses proteins from the core, NS3, and NS4 regions. The 3.0G ELISA includes the protein from the NS5 region. The

necessity of detecting antibodies to viral **envelope proteins** (E1 and E2) and to different genotype samples has been demonstrated previously. In this study we have attempted to improve the sensitivity of the anti-HCV assay by developing a single multiple-epitope fusion antigen (MEFA; MEFA-6) which incorporates all of the major immunodominant epitopes from the seven functional regions of the HCV genome. A nucleic acid sequence consisting of proteins from the viral core, E1, E2, NS3, NS4, and NS5 regions and different subtype-specific regions of the NS4 region was constructed, cloned, and expressed in yeast. The epitopes present on this antigen can be detected by epitope-specific monoclonal and polyclonal antibodies. In a competition assay, the MEFA-6 protein competed with 83 to 96% of genotype-specific antibodies from HCV genotype-specific peptides. This recombinant antigen was subsequently used to design an anti-HCV chemiluminescent immunoassay. We designed our assay using a monoclonal anti-human IgG antibody bound to the solid phase. Because MEFA-6 is fused with human superoxide dismutase (h-SOD), we used an anti-human superoxide dismutase, di-Me acridinium ester-labeled **monoclonal antibody** for detection. Our results indicate that MEFA-6 exposes all of the major immunogenic epitopes. Its excellent sensitivity and specificity for the detection of clin. seroconversion are demonstrated by this assay.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:117461 CAPLUS

DOCUMENT NUMBER: 130:324135

TITLE: New monoclonal antibodies against a recombinant second

**envelope protein** of hepatitis C virus

AUTHOR(S): Inudoh, Michiharu; Kato, Nobuyuki; Tanaka, Yuetsu  
CORPORATE SOURCE: Virology Division, National Cancer Center Research Institute, Chuo-ku, Tokyo, 104-0045, Japan

SOURCE: Microbiology and Immunology (1998), 42(12), 875-877  
CODEN: MIIMDV; ISSN: 0385-5600

PUBLISHER: Center for Academic Publications Japan

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To study the immunol. features of the hepatitis C virus (HCV) **envelope protein** (E2 protein), new specific **monoclonal antibodies** (mAbs) were generated. WKA/H rats were immunized with syngeneic cells infected with a vaccinia virus expressing the E2 protein and with sol. E2 protein obtained from Chinese hamster ovary cells with a plasmid-based expression system. By screening hybridoma cells obtained from spleen cells of the immunized rats, three specific mAbs were obtained. One mAb was reactive to a peptide corresponding to the hypervariable region 1 (HVR1) in E2 protein, while the others reacted to regions outside HVR1. The significance of these antibodies for the diagnosis of HCV infection as well as for anal. of the structure of the HCV E2 protein will be discussed.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 22 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:313394 CAPLUS  
DOCUMENT NUMBER: 129:107767  
TITLE: Isolation and characterization of human monoclonal antibodies against hepatitis C virus envelope glycoproteins  
AUTHOR(S): Da Silva Cardoso, Marcia; Siemoneit, Karl; Sturm, Daniela; Krone, Christoph; Moradpour, Darius; Kubanek, Bernhard  
CORPORATE SOURCE: Blood Transfusion Service of Baden-Wurttemberg and Department of Transfusion Medicine, University of Ulm, Germany  
SOURCE: Journal of Medical Virology (1998), 55(1), 28-34  
CODEN: JMVIDB; ISSN: 0146-6615  
PUBLISHER: Wiley-Liss, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The isolation and characterization of human **monoclonal antibodies** (humAbs) against the hepatitis C virus (HCV) glycoproteins E1 and E2 are described. B-cells from blood donors with anti-HCV were transformed with Epstein-Barr virus. The supernatants of the resulting lymphoblastoid clones were screened by ELISA with an ext. of cells infected with a recombinant vaccinia virus RMPA95 expressing the **envelope proteins** E1 and E2 of an HCV genotype 1a virus (H strain). Pos. clones were fused to the heteromyeloma cell line K6H6/B5. Fifteen heterohybridoma cell lines have been established. The specificity of the isolated humAbs was detd. both by ELISA and Western blot assays. Several recombinant exts. expressing either the E1 or E2 protein or truncated forms were used in an attempt to map the epitopes on the viral glycoproteins. Some of the humAbs were used successfully for immunofluorescence investigation of transfected cells. Seven specific anti-E2 humAbs, which react with the **envelope protein 2** of genotype 1a and 1b isolates, were characterized.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 23 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:7577 CAPLUS  
DOCUMENT NUMBER: 128:87733  
TITLE: Humoral immune response to the E2 protein of hepatitis G virus is associated with long-term recovery from infection and reveals a high frequency of hepatitis G virus exposure among healthy blood donors  
AUTHOR(S): Tacke, Michael; Schmolke, Susanne; Schlueter, Volker; Saulea, Silvia; Esteban, Juan I.; Tanaka, Eiji; Kiyosawa, Kendo; Alter, Harvey J.; Schmitt, Urban; Hess, Georg; Ofenloch-Haehnle, Beatus; Engel, Alfred M.  
CORPORATE SOURCE: Boehringer Mannheim GmbH, R & D Infectious Diseases, Penzberg, Germany  
SOURCE: Hepatology (Philadelphia) (1997), 26(6), 1626-1633  
CODEN: HPTLD9; ISSN: 0270-9139  
PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The second **envelope protein** (E2) of the hepatitis G virus (HGV) was expressed in Chinese hamster ovary (CHO) cells and showed a mol. wt. of approx. 60-70 kDa, with 15-25 kDa of the size contributed by N-linked glycosylation. An ELISA using HGV-E2 was developed to test for antibodies to this protein (anti-E2) in human sera. High sensitivity was achieved by developing **monoclonal antibodies** (mAbs) to HGV-E2, which were used as capture antibodies in the ELISA. The authors' studies revealed that 16% of healthy Spanish blood donors were exposed to HGV, indicating that addnl. routes of viral transmission besides parenteral exposure might exist. An even higher prevalence of exposure to HGV (52-73%) was found in several groups at risk of parenteral exposure to infectious agents, i.e., i.v. drug users, transfusion history, hemophiliacs, and hepatitis C virus (HCV)-pos. patients. Most anti-E2-pos. patients were HGV-RNA-neg. and vice versa, indicating an inverse correlation of these 2 viral markers. A panel of 16 post-transfusion patients followed for up to 16 yr revealed that patients who develop an anti-E2 response become HGV-RNA-neg., while patients who do not develop anti-E2 are persistently infected. Immunity to HGV seems to be long-lasting, because circulating antibody to E2 could still be detected 14 yr after seroconversion. Sequence comparisons showed that E2 is highly conserved among isolates collected worldwide, indicating that immune escape variants are not common in HGV infections. This reflects on a mol. level why HGV infections usually are cleared spontaneously by the host. However, possible mechanisms of HGV persistence, as found in some patients, remain to be elucidated.

L9 ANSWER 24 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:295079 CAPLUS  
DOCUMENT NUMBER: 124:352673  
TITLE: Recombinant production and purification of hepatitis C

INVENTOR(S): virus **envelope proteins** for diagnostic and therapeutic use  
Maertens, Geert; Bosman, Fons; De Martynoff, Guy; Buyse, Marie-Ange

PATENT ASSIGNEE(S): Innogenetics N.V., Belg.

SOURCE: PCT Int. Appl., 146 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent  
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604385	A2	19960215	WO 1995-EP3031	19950731
WO 9604385	A3	19960307		
W:	AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA			
RW:	KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE,			

SN, TD, TG

CA 2172273	AA	19960215	CA 1995-2172273	19950731
AU 9533824	A1	19960304	AU 1995-33824	19950731
AU 708174	B2	19990729		
EP 721505	A1	19960717	EP 1995-930434	19950731
EP 721505	B1	20020508		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,

SE

JP 09503396	T2	19970408	JP 1995-506189	19950731
BR 9506059	A	19971028	BR 1995-6059	19950731
SG 71728	A1	20000418	SG 1997-3877	19950731
AT 217345	E	20020515	AT 1995-930434	19950731
EP 1211315	A1	20020605	EP 2002-3643	19950731

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

IE

ES 2174957	T3	20021116	ES 1995-930434	19950731
US 6150134	A	20001121	US 1996-612973	19960311
US 6245503	B1	20010612	US 1997-927597	19970911
US 2003036110	A1	20030220	US 2001-899303	20010706
US 2002182706	A1	20021205	US 2001-973025	20011010

PRIORITY APPLN. INFO.:

	EP 1994-870132	A	19940729
	EP 1995-930434	A3	19950731
	WO 1995-EP3031	W	19950731
	US 1996-612973	A3	19960311
	US 1997-928017	B3	19970911

AB **Envelope proteins** E1 and E2 of hepatitis C virus (**HCV**), their recombinant prodn. and purifn., their fragments and engineered derivs., their antigenic epitope peptides, their **monoclonal antibodies**, and their use for diagnostic and therapeutic means are provided. A method is described for purifying recombinant **HCV** single or specific oligomeric **envelope proteins**, characterized in that upon lysing the transformed host cells to isolate the recombinantly expressed protein a disulfide bond cleavage or redn. step is carried out with a disulfide bond cleavage agent (such as dithiothreitol and/or Empigen BB) and an SH group protecting agent (such as N-ethylmaleimide). Various forms of the E1 and E2 proteins are constructed by std. genetic techniques using vaccinia virus recombination vectors; such proteins are specific for various **HCV** genotypes, may delete the hydrophobic region from E1, or remove various glycosylation sites; they may also add factor Xa cleavage sites and His6 tags for improved purifn. Epitope (such as F, G, H, and I) peptides are used to generate **monoclonal antibodies** and to monitor disease progression in patients. Furthermore, the **HCV** E1 protein and peptides are used for prognosing and monitoring the clin. effectiveness and/or clin. outcome of **HCV** treatment.

L9 ANSWER 25 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:152827 CAPLUS

DOCUMENT NUMBER: 124:229245

TITLE: A quantitative test to estimate neutralizing antibodies to the hepatitis C virus: Cytofluorimetric assessment of envelope glycoprotein 2 binding to target cells

AUTHOR(S): Rosa, Domenico; Campagnoli, Susanna; Moretto, Carlo; Guenzi, Eric; Cousens, Lawrence; Chin, Michael; Dong, Christine; Weiner, Amy J.; Lau, Johnson Y. N.; et al.

CORPORATE SOURCE: Chiron-Biocrine, Immunobiology Research Inst., Siena, 53100, Italy

SOURCE: Proceedings of the National Academy of Sciences of  
the

United States of America (1996), 93(5), 1759-63  
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hepatitis C virus (HCV) is a major cause of chronic hepatitis.  
The virus does not replicate efficiently in cell cultures, and it is  
therefore difficult to assess infection-neutralizing antibodies and to  
evaluate protective immunity in vitro. To study the binding of the  
HCV envelope to cell-surface receptors, we developed an assay to  
assess specific binding of recombinant **envelope proteins**  
to human cells and neutralization thereof. HCV recombinant  
**envelope proteins** expressed in various systems were  
incubated with human cells, and binding was assessed by flow cytometry  
using anti-envelope antibodies. Envelope glycoprotein 2 (E2) expressed

in

mammalian cells, but not in yeast or insect cells, binds human cells with  
high affinity ( $K_d$  approx.  $10^{-8}$  M). We then assessed antibodies able to  
neutralize E2 binding in the sera of both vaccinated and carrier  
chimpanzees, as well as in the sera of humans infected with various  
HCV genotypes. Vaccination with recombinant **envelope**  
**proteins** expressed in mammalian cells elicited high titers of  
neutralizing antibodies that correlated with protection from HCV  
challenge. HCV infection does not elicit neutralizing  
antibodies in most chimpanzees and humans, although low titers of  
neutralizing antibodies were detectable in a minority of infections. The  
ability to neutralize binding of E2 derived from the HCV-1  
genotype was equally distributed among sera from patients infected with  
HCV genotypes 1, 2, and 3, demonstrating that binding of E2 is  
partly independent of E2 hypervariable regions. However, a mouse  
**monoclonal antibody** raised against the E2 hypervariable  
region 1 can partially neutralize binding of E2, indicating that at least  
two neutralizing epitopes, one of which is hypervariable, should exist on  
the E2 protein. The neutralization-of-binding assay described will be  
useful to study protective immunity to HCV infection and for  
vaccine development.

L9 ANSWER 26 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:42631 CAPLUS

DOCUMENT NUMBER: 124:84303

TITLE: High efficiency prokaryotic expression and  
purification of a portion of the hepatitis C core  
protein and analysis of the immune response to  
recombinant protein in BALB/c mice

AUTHOR(S): Hitomi, Y.; McDonnell, W. M.; Baker, J. R., Jr.;  
Askari, F. K.

CORPORATE SOURCE: Dep. Internal Medicine, Univ. Michigan, Ann Arbor,  
MI,

48109-0680, USA

SOURCE: Viral Immunology (1995), 8(2), 109-19

CODEN: VIIMET; ISSN: 0882-8245

PUBLISHER: Liebert

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hepatitis C virus (HCV) produces chronic persistent liver  
infection in 1-2% of the U.S. population and is the leading cause of end  
stage liver disease in patients presenting for liver transplantation at  
our center. Efforts to cure persistent HCV infection are

frequently unsuccessful, so the development of a HCV vaccine is a high priority. HCV envelope proteins are hypervariable so prodn. of a recombinant surface antigen vaccine such as is available for hepatitis B is not likely to confer widespread, high level protective immunity. As the most highly conserved structural protein in the HCV genome, the core protein is one reasonable target for vaccine prodn. Presented here are data on the manuf. of recombinant core protein contg. partial carboxy terminus deletions in an effort to increase the efficiency of core expression. The maltose binding protein (MBP) and glutathione S-transferase (GST) protein prokaryotic expression systems were used to study two different constructs, expressing the first 140 and 163 amino acids of the core region. Deletion of the 23 amino acids (aa) from aa141-163 led to a marked increase in the efficiency of protein prodn. from <1 to 3-4 mg/L for both systems studied. Protein purifn. was accomplished using affinity chromatog. (MBP) or inclusion body isolation (GST) as detd. by SDS-PAGE gels and immunotransblot with HCV core protein-specific monoclonal antibody. Finally, the immune response to recombinant protein was assessed in BALB/c mice using a MBP HCV core fusion protein and an ELISA developed using GST HCV core protein as a target. In all mice of this strain, serum anti-HCV core antibody titer increased to 10<sup>-4</sup>, two logs above background, following immunization in conjunction with Freund's complete adjuvant. These results represent an encouraging first step toward prodn. of a core protein vaccine. Recombinant core protein is a useful tool to study the immune response to core protein and may be useful to further study the epidemiol. and biol. of the HCV virus.

L9 ANSWER 27 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:698202 CAPLUS  
DOCUMENT NUMBER: 121:298202  
TITLE: Processing of E1 and E2 glycoproteins of hepatitis C virus expressed in mammalian and insect cells  
AUTHOR(S): Matsuura, Yoshiharu; Suzuki, Tetsuro; Suzuki, Ryosuke;  
Sato, Mitsuru; Aizaki, Hideki; Saito, Izumu; Miyamura, Tatsuo  
CORPORATE SOURCE: Dep. Virology II, Natl. Inst. Health, Tokyo, 162, Japan  
SOURCE: Virology (1994), 205(1), 141-50 *Nb J.*  
CODEN: VIRLAX; ISSN: 0042-6822  
PUBLISHER: Academic  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Processing of the envelope glycoproteins (E1 and E2) of hepatitis C virus (HCV) was investigated by using cDNA clones covering the structural and part of the nonstructural (NS) protein regions. The cDNA clones expressed in mammalian and insect cells were immunopptd. by serum of a hepatitis C patient and by monoclonal and polyclonal antibodies riased against the recombinant proteins expressed in insect cells or Escherichia coli. The E2 protein expressed in both insect and mammalian cells was a glycoprotein of 60 kDa (gp60) and removal of the sugar residues by N-glycanase yielded 38- and 40-kDa proteins. Pulse-chase

expts. revealed that efficient expression and processing of the **envelope proteins** required coexpression with the flanking core and NS2 proteins. Not only E1 and E2 proteins but also NS2 and NS3 proteins were copptd. by anti-E1 or anti-E2 **monoclonal antibody** in the cells infected with the recombinant baculovirus expressing structural and NS proteins (NS2 and NS3), while only the NS3 protein was pptd. by anti-NS3 antibody. The assocn. of E1 and E2 proteins was not influenced by the presence of a reducing agent and was still obsd. in the cells coinfectd with the deletion mutants lacking both internal and C-terminal hydrophobic regions of each protein. Furthermore, the truncated forms of the E1 and E2 proteins were secreted into the culture supernatant and some of them were still assocd. with each other.

L9 ANSWER 28 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:478160 CAPLUS  
DOCUMENT NUMBER: 121:78160  
TITLE: Hepatitis C virus particle detected by immunoelectron microscopic study  
AUTHOR(S): Kaito, Masahiko; Watanabe, Shozo; Tsukiyama-Kohara, Kyoko; Yamaguchi, Kenjiro; Kobayashi, Yoshinao; Konishi, Masayoshi; Yokoi, Masato; Ishida, Satoshi; Suzuki, Shiro; Kohara, Michinori  
CORPORATE SOURCE: Sch. Med., Mie Univ., Mie, 514, Japan  
SOURCE: Journal of General Virology (1994), 75(7), 1755-60  
CODEN: JGVIAY; ISSN: 0022-1317  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB To clarify the morphol. of hepatitis C virus (HCV), an indirect immunogold electron microscope study was carried out on two plasma samples with high HCV RNA titers using polyclonal and **monoclonal antibodies** specific to the putative **HCV envelope protein**. Spherical virus-like particles 55 to 65 nm in diam. with spike-like projections, were found in 1.14 to 1.6 g/mL fractions after sucrose d. gradient centrifugation. These particles were found only in **HCV**-infected blood donors and had morphol. features similar to those of flaviviruses. Moreover, these particles specifically reacted with the polyclonal and **monoclonal antibodies** to the putative **HCV envelope protein**. This is the first known report in which the morphol. of the **HCV** particle is clearly shown.

L9 ANSWER 29 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1993:184510 CAPLUS  
DOCUMENT NUMBER: 118:184510  
TITLE: Detection of hepatitis B virus in plasma using flow cytometric analyses of polymerase chain reaction-amplified DNA incorporating digoxigenin-11-dUTP  
AUTHOR(S): Yang, Gang; Ulrich, Paul P.; Aiyer, Ramani A.; Rawal, Bhupat D.; Vyas, Girish N.  
CORPORATE SOURCE: Dep. Lab. Med., Univ. California, San Francisco, CA, 94143-0134, USA  
SOURCE: Blood (1993), 81(4), 1083-8  
CODEN: BLOOAW; ISSN: 0006-4971  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Blood donations are routinely screened by multiple serol. assays for

antigens/antibodies assocd. with infection by blood-borne viruses, including hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency viruses (HIV-1 and HIV-2), and human T-cell lymphotropic virus (HTLV-1 and HTLV-II). A direct detection of these viruses would be more effective for the prevention of transfusion-transmitted infections than the indirect measurement of the variable host immune response to these agents. Because the polymerase chain reaction (PCR) for viral gene amplification offers the most sensitive and direct means of detecting viruses in blood, the authors have developed a nonisotopic PCR procedure for the detection of HBV, chosen as a prototype.

The problems, common to previously described PCR methods, of nucleic acid extn. and inhibition of the PCR by plasma proteins were overcome by isolation of HBV from plasma by means of 450- $\mu$ m polystyrene beads covalently coated with **monoclonal antibody** to the Pre-S1 region of the viral **envelope protein**.

Detergent lysis and proteinase K digestion of the immunocaptured virions isolated from plasma released the HBV DNA. A modified PCR-amplification protocol, incorporating digoxigenin-labeled dUTP in the amplified gene products followed by hybridization with a specific biotinylated oligonucleotide probe bound to streptavidin-coated 2.8- $\mu$ m magnetic beads, allowed flow cytometric analyses of HBV-specific PCR products by means of antibodies to digoxigenin labeled with fluorescein isothiocyanate. The endpoint serial dilns. of pedigreed human plasma samples contg. chimpanzee infectious dose (CID50) of 107 for adw and

CID50

of 107.5 for the ayw subtypes were compared in repeated testing of PCR products by the authors immunoreactive bead (PCR-IRB) assay. HBV DNA was consistently detected in a 5 .times. 10-10 diln. of each sample. In testing 20 coded specimens of blood donors, with or without serol.

markers

of HBV infection, the PCR-IRB was specific and more sensitive than the

PCR

analyses by slot blot hybridization with radioactive probe. The PCR-IRB assay can be adapted for simultaneous detection of multiple blood-borne viruses by an automated flow cytometric anal. system.

L9 ANSWER 30 OF 30 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1990:194997 CAPLUS

DOCUMENT NUMBER: 112:194997

TITLE: Immunoaffinity purification and characterization of the **envelope protein** E1 of hog cholera virus

AUTHOR(S): Wensvoort, G.; Boonstra, J.; Bodzinga, B. G.

CORPORATE SOURCE: Dep. Virol., Cent. Vet. Inst., Lelystad, 8200 AJ, Neth.

SOURCE: Journal of General Virology (1990), 71(3), 531-40  
CODEN: JGVIAY; ISSN: 0022-1317

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The **envelope protein** E1 of hog cholera virus (HCV) was isolated by immunoaffinity purifn. with **monoclonal antibodies** (MAbs) directed against HCV. E1 consisted of a doublet of glycoproteins which varied in size from 51K to 56K between the 3 strains tested. E1 contains major antigenic determinants of HCV which are conserved, and are involved in neutralization by MAbs. In infected cells, E1 was found always connected with a glycoprotein of 31K. When N-linked glycans were removed, E1 had a polypeptide backbone of approx. 47K. After proteolytic cleavage of E1 with Staphylococcus protease V8 and after electrophoresis

and electrotransfer, peptide fragments contg. different antigenic domains  
of E1 were detected with MAbs directed against HCV.

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STN INTERNATIONAL LOGOFF AT 11:42:42 ON 02 APR 2003

L5 ANSWER 42 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:569053 CAPLUS

DOCUMENT NUMBER: 117:169053

TITLE: Glycosylated envelope protein of hepatitis C virus expressed in animal cells

AUTHOR(S): Matsuura, Yoshiharu; Harada, Shizuko; Suzuki, Ryousuke; Watanabe, Yushiro; Inoue, Yoshimichi; Miyamura, Tatsuo; Saito, Izumu

CORPORATE SOURCE: Dep. Vet. Sci., Natl. Inst. Health, Tokyo, 208, Japan  
SOURCE: Vaccines 92: Mod. Approaches New Vaccines Incl. Prev.

AIDS [Annu. Meet.], 9th (1992), 309-14. Editor(s): Brown, Fred. Cold Spring Harbor Lab. Press: Cold Spring Harbor, N. Y.

CODEN: 57WXAL

DOCUMENT TYPE: Conference

LANGUAGE: English

TI Glycosylated envelope protein of hepatitis C virus expressed in animal cells

SO Vaccines 92: Mod. Approaches New Vaccines Incl. Prev. AIDS [Annu. Meet.],

9th (1992), 309-14. Editor(s): Brown, Fred. Publisher: Cold Spring Harbor

Lab. Press, Cold Spring Harbor, N. Y.

CODEN: 57WXAL

AU Matsuura, Yoshiharu; Harada, Shizuko; Suzuki, Ryousuke; Watanabe, Yushiro;

Inoue, Yoshimichi; Miyamura, Tatsuo; Saito, Izumu

AB The putative envelope protein of hepatitis C virus (HCV) was expressed in insect cells using a baculovirus expression vector and in monkey COS cells

under the control of exogenous promoters. The expressed envelope proteins, identified by immunoblot anal. using sera of chronic hepatitis C

patients, were a series of glycoproteins of 35-24 kD (gp35-24) in the insect cells and a single species of glycoprotein of 35 kD (gp35) in monkey cells. Because removal of the sugar residues of the proteins expressed in insect and mammalian cells yielded an apparently identical 22-kD protein, the size difference was due to the degree of glycosylation.

The envelope proteins expressed in these cells were produced by common specific cleavage from the precursor protein. The cleavage positions of the envelope protein were mapped approx. at amino acids 190 and 380. The gp35-24 expressed in insect cells was used for detection of

**antibody against HCV envelope protein** in patients' sera. The results showed that almost all patients having the

anti-E **antibody**, i.e., 4-11% of hepatitis C patients, were either cured or well-controlled, suggesting that the presence of anti-E **antibody** is important in the control of the diseases

L5 ANSWER 40 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:4188 CAPLUS

DOCUMENT NUMBER: 120:4188

TITLE: Characterization of hepatitis C virus envelope glycoprotein complexes expressed by recombinant vaccinia viruses

AUTHOR(S): Ralston, Robert; Thudium, Kent; Berger, Kim; Kuo, Carol; Gervase, Barbara; Hall, John; Selby, Mark; Kuo,

George; Houghton, Michael; Choo, Qui Lim

CORPORATE SOURCE: Chiron Corp., Emeryville, CA, 94608, USA

SOURCE: Journal of Virology (1993), 67(11), 6753-61

CODEN: JOVIAM; ISSN: 0022-538X

DOCUMENT TYPE: Journal

LANGUAGE: English

TI Characterization of hepatitis C virus envelope glycoprotein complexes expressed by recombinant vaccinia viruses

SO Journal of Virology (1993), 67(11), 6753-61

CODEN: JOVIAM; ISSN: 0022-538X

AU Ralston, Robert; Thudium, Kent; Berger, Kim; Kuo, Carol; Gervase, Barbara;

Hall, John; Selby, Mark; Kuo, George; Houghton, Michael; Choo, Qui Lim

AB The authors constructed recombinant vaccinia virus vectors for expression of the structural region of hepatitis C virus (HCV). Infection of mammalian cells with a vector (vv/HCV1-906) encoding C-E1-E2-NS2 generated

major protein species of 22 kDa (C), 33 to 35 kDa (E1), and 70 to 72 kDa (E2), as obsd. previously with other mammalian expression systems. The bulk of the E1 and E2 expressed by vv/HCV1-906 was integrated into endoplasmic reticulum membranes as core-glycosylated species, suggesting that these E1 and E2 species represent intracellular forms of the HCV envelope proteins. HCV E1 and E2 formed

E1-E2 complexes which were pptd. by either anti-E1 or anti-E2 serum and which sedimented at approx. 15 S on glycerol d. gradients. No evidence

of intermol. disulfide bonding between E1 and E2 was detected. E1 and E2 were copurified to approx. 90% purity by mild detergent extn., followed

by chromatog. on Galanthus nivalus lectin-agarose and DEAE-Fractogel. Immunization of chimpanzees with purified E1-E2 generated high titers of anti-E1 and anti-E2 antibodies. Further studies demonstrated that purified E1-E2 complexes were recognized at high frequency by HCV+ human sera and generated protective immunity in chimpanzees, suggesting that these purified HCV envelope proteins display native HCV epitopes.

L5 ANSWER 2 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:545219 CAPLUS

DOCUMENT NUMBER: 137:123799

TITLE: Enhancement of the immune response generated against hepatitis C virus envelope proteins after DNA vaccination with polyprotein-encoding plasmids

AUTHOR(S): Duenas-Carrera, Santiago; Alvarez-Lajonchere, Liz; Alvarez-Obregon, Julio Cesar; Perez, Anna; Acosta-Rivero, Nelson; Vazquez, Dania Marcia; Martinez, Gillian; Vina, Ariel; Pichardo, Dagmara; Morales, Juan

CORPORATE SOURCE: Departamento Hepatitis C, Division de Vacunas, Centro de Ingenieria Genetica y Biotecnologia, Havana City, Cuba

SOURCE: Biotechnology and Applied Biochemistry (2002), 35(3), 205-212

CODEN: BABIEC; ISSN: 0885-4513

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

TI Enhancement of the immune response generated against hepatitis C virus envelope proteins after DNA vaccination with polyprotein-encoding plasmids

SO Biotechnology and Applied Biochemistry (2002), 35(3), 205-212

CODEN: BABIEC; ISSN: 0885-4513

AU Duenas-Carrera, Santiago; Alvarez-Lajonchere, Liz; Alvarez-Obregon, Julio Cesar; Perez, Anna; Acosta-Rivero, Nelson; Vazquez, Dania Marcia; Martinez, Gillian; Vina, Ariel; Pichardo, Dagmara; Morales, Juan

AB Plasmids expressing variants of the hepatitis C virus (HCV) core, E1 and E2 proteins individually or as polyproteins were administered to BALB/c mice. All plasmids induced a detectable and specific **antibody** response. **Antibody** titers against core, E1 and E2 proteins, 19 wk after primary immunization, ranged from 1:50 to 1:4500 depending on

the inoculated plasmid and the HCV antigen evaluated. Constructs expressing **HCV envelope proteins** as polyprotein variants including the core amino acid region induced statistically stronger **antibody** responses than plasmids encoding individual E1 and E2 proteins. Particularly, the pIDKE2 plasmid, expressing the first 650 amino acids in the viral polyprotein, induced a potent and multispecific **antibody** and lymphoproliferative response against HCV core, E1 and E2 proteins. Anti-E2 **antibodies** generated by pIDKE2 immunization were cross-reactive to hypervariable region-1 peptides from different genotypes. Immunization with the pIDKE2 also generated a pos. cellular immune response against the core antigen, detd. by interferon-.gamma. enzyme-linked immunospot (ELISPOT) assay, and induced detectable levels of interferon-.gamma. but not interleukin-4 in vaccinated mice. The detection of both **antibody** and cytotoxic T-lymphocyte responses, potentially targeted to circulating or cell-infecting virions resp., in mice vaccinated with the pIDKE2 plasmid is very attractive for the effective eradication of HCV infection.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L5 ANSWER 24 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:63194 CAPLUS

DOCUMENT NUMBER: 130:236367

TITLE: Viral persistence, **antibody** to E1 and E2, and hypervariable region 1 sequence stability in hepatitis C virus-inoculated chimpanzees

AUTHOR(S): Bassett, Suzanne E.; Thomas, David L.; Brasky, Kathleen M.; Lanford, Robert E.

CORPORATE SOURCE: Department of Virology and Immunology, Southwest Foundation for Biomedical Research, San Antonio, TX, 78227, USA

SOURCE: Journal of Virology (1999), 73(2), 1118-1126  
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

TI Viral persistence, **antibody** to E1 and E2, and hypervariable region 1 sequence stability in hepatitis C virus-inoculated chimpanzees

SO Journal of Virology (1999), 73(2), 1118-1126  
CODEN: JOVIAM; ISSN: 0022-538X

AU Bassett, Suzanne E.; Thomas, David L.; Brasky, Kathleen M.; Lanford, Robert E.

AB The relationship of viral persistence, the immune response to hepatitis C virus (HCV) **envelope proteins**, and envelope sequence variability was examd. in chimpanzees. **Antibody** reactivity to the **HCV envelope proteins** E1 or E2 was detected by ELISA in >90% of a human serum panel. Although the ELISAs appeared to be sensitive indicators of HCV infection in human serum

panels, the results of a cross-sectional study revealed that a low percentage of HCV-inoculated chimpanzees had detectable **antibody** to E1 (22%) and E2 (15%). Viral clearance, which was recognized in 28 (61%) of the chimpanzees, was not assocd. with an **antibody** response to E1 or E2. On the contrary, **antibody** to E2 was obsd. only in viremic chimpanzees. A longitudinal study of animals that

cleared the viral infection or became chronically infected confirmed the low level

of **antibody** to E1, E2, and the HVR-1. In 10 chronically infected animals, the sequence variation in the E2 hypervariable region (HVR-1) was minimal and did not coincide with **antibody** to E2 or to the HVR-1. In addn., low nucleotide and amino acid sequence variation was obsd. in the E1 and E2 regions from two chronically infected chimpanzees. These results suggest that mechanisms in addn. to the emergence of HVR-1 **antibody** escape variants are involved in maintaining viral persistence.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS

FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L5 ANSWER 23 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:117461 CAPLUS

DOCUMENT NUMBER: 130:324135

TITLE: New monoclonal **antibodies** against a recombinant second envelope protein of hepatitis C virus

AUTHOR(S): Inudoh, Michiharu; Kato, Nobuyuki; Tanaka, Yuetsu  
CORPORATE SOURCE: Virology Division, National Cancer Center Research Institute, Chuo-ku, Tokyo, 104-0045, Japan

SOURCE: Microbiology and Immunology (1998), 42(12), 875-877  
CODEN: MIIMDV; ISSN: 0385-5600

PUBLISHER: Center for Academic Publications Japan

DOCUMENT TYPE: Journal

LANGUAGE: English

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SO Microbiology and Immunology (1998), 42(12), 875-877  
CODEN: MIIMDV; ISSN: 0385-5600

AU Inudoh, Michiharu; Kato, Nobuyuki; Tanaka, Yuetsu

AB To study the immunol. features of the hepatitis C virus (HCV) **envelope protein** (E2 protein), new specific monoclonal **antibodies** (mAbs) were generated. WKA/H rats were immunized with syngeneic cells infected with a vaccinia virus expressing the E2 protein and with sol. E2 protein obtained from Chinese hamster ovary cells with a plasmid-based expression system. By screening hybridoma cells obtained from spleen cells of the immunized rats, three specific mAbs were obtained. One mAb was reactive to a peptide corresponding to the hypervariable region 1 (HVR1) in E2 protein, while the others reacted to regions outside HVR1. The significance of these **antibodies** for the diagnosis of HCV infection as well as for anal. of the structure of the HCV E2 protein will be discussed.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS

FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L5 ANSWER 22 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:129948 CAPLUS

DOCUMENT NUMBER: 130:336667

TITLE: Immunodominant B-cell domains of hepatitis C virus envelope proteins E1 and E2 identified during early and late time points of infection

AUTHOR(S): Zibert, Andree; Kraas, Wolfgang; Ross, R. Stefan; Meisel, Helga; Lechner, Sabine; Jung, Gunther; Roggendorf, Michael

CORPORATE SOURCE: Institut fur Virologie, Universitätsklinikum Essen, Essen, Germany

SOURCE: Journal of Hepatology (1999), 30(2), 177-184

CODEN: JOHEEC; ISSN: 0168-8278

PUBLISHER: Munksgaard International Publishers Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

TI Immunodominant B-cell domains of hepatitis C virus envelope proteins E1 and E2 identified during early and late time points of infection

SO Journal of Hepatology (1999), 30(2), 177-184

CODEN: JOHEEC; ISSN: 0168-8278

AU Zibert, Andree; Kraas, Wolfgang; Ross, R. Stefan; Meisel, Helga; Lechner, Sabine; Jung, Gunther; Roggendorf, Michael

AB Background/Aims: the authors characterized immunoreactive B-cell domains of hepatitis C virus (HCV) **envelope proteins**

E1 and E2 by a peptide ELISA using sera of patients who were infected by the same isolate of HCV (HCV-AD78). Methods: Fifty-four overlapping peptides which corresponded to the sequence of E1 and E2 of isolate HCV-AD78 were used to detect specific **antibodies**. Three groups of HCV-AD78 related sera were analyzed. Two groups were from sera obtained at early time points of infection (months 4-15) from patients

who

later resolved infection (group A), or who later developed chronic disease

(group B). Group C sera were from later time points of chronic disease. As a control, sera of chronic HCV patients who did not have HCV-AD78 infection were also analyzed (group D). Results: In group A, 25 of the

54

peptides produced OD405 above the cut-off, whereas 17 peptides produced such values in group B. Only 10 and 3 peptides yielded such values in groups C and D, resp. The overall prevalence of **antibodies** against peptides was high in the early phase of infection (means of 28.7% and 25.9% in groups A and B, resp.). At later time points of chronic infection (group C), the overall prevalence was lower (mean 18.6%).

Group

D sera produced the lowest overall prevalence (mean 13.2%). Three peptides, covering aa271-290, aa481-500 and aa551-570, were recognized significantly more frequently by group A sera than group B sera.

Conclusions: the authors conclude that more linear epitopes of the HCV envelope are recognized with a high prevalence of **antibodies**, as was suggested previously. However, most B-cell domains of the HCV envelope induce a similarly high **antibody** response in patients who resolve infection or develop chronic disease.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L5 ANSWER 21 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:325806 CAPLUS

DOCUMENT NUMBER: 130:349392

TITLE: Diagnostic and medicinal use of host-derived proteins  
binding hepatitis C virus

INVENTOR(S): Maertens, Geert; Depla, Erik

PATENT ASSIGNEE(S): Innogenetics N.V., Belg.

SOURCE: PCT Int. Appl., 58 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9924054	A1	19990520	WO 1998-EP7107	19981106
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2305715	AA	19990520	CA 1998-2305715	19981106
AU 9915610	A1	19990531	AU 1999-15610	19981106
EP 1028742	A1	20000823	EP 1998-959859	19981106
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2001522809	T2	20011120	JP 2000-520142	19981106
PRIORITY APPLN. INFO.:			EP 1997-870178 A	19971106
			WO 1998-EP7107 W	19981106
TI	Diagnostic and medicinal use of host-derived proteins binding hepatitis C virus			
SO	PCT Int. Appl., 58 pp. CODEN: PIXXD2			
IN	Maertens, Geert; Depla, Erik			
AB	The finding that the human proteins annexin V, tubulin and apolipoprotein B bind to the hepatitis C virus envelope proteins E1 and/or E2 and the usage of these human proteins to diagnose and treat an infection with hepatitis C virus are described. The usage of the latter proteins to enrich <b>HCV envelope proteins</b> and mols. which inhibit binding of HCV to these human proteins, as well as vaccines employing the E1 and/or E2 binding domains are also disclosed.			
REFERENCE COUNT:	5	THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE		
FORMAT				

L5 ANSWER 12 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:799830 CAPLUS

DOCUMENT NUMBER: 134:70078

TITLE: Human monoclonal **antibodies** that inhibit binding of hepatitis C virus E2 protein to CD81 and recognize conserved conformational epitopes

AUTHOR(S): Hadlock, Kenneth G.; Lanford, Robert E.; Perkins, Susan; Rowe, Judy; Yang, Qing; Levy, Shoshana;

Pileri,

CORPORATE SOURCE: Piero; Abrignani, Sergio; Fountg, Steven K. H. Department of Pathology, Stanford University, Stanford, CA, USA

SOURCE: Journal of Virology (2000), 74(22), 10407-10416

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

TI Human monoclonal **antibodies** that inhibit binding of hepatitis C virus E2 protein to CD81 and recognize conserved conformational epitopes

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CODEN: JOVIAM; ISSN: 0022-538X

AU Hadlock, Kenneth G.; Lanford, Robert E.; Perkins, Susan; Rowe, Judy; Yang,

Qing; Levy, Shoshana; Pileri, Piero; Abrignani, Sergio; Fountg, Steven K. H.

AB The intrinsic variability of hepatitis C virus (HCV)

**envelope proteins** E1 and E2 complicates the identification of protective **antibodies**. In an attempt to identify **antibodies** to E2 proteins from divergent HCV isolates, we produced HCV E2 recombinant proteins from individuals infected with

HCV

genotypes 1a, 1b, 2a, and 2b. These proteins were then used to characterize 10 human monoclonal **antibodies** (HMABs) produced from peripheral B cells isolated from an individual infected with HCV genotype 1b. Nine of the **antibodies** recognize conformational epitopes within HCV E2. Six HMABs identify epitopes shared among HCV genotypes 1a, 1b, 2a, and 2b. Six, including five broadly reactive

HMABs,

could inhibit binding of HCV E2 of genotypes 1a, 1b, 2a, and 2b to human CD81 when E2 and the **antibody** were simultaneously exposed to CD81. Surprisingly, all of the **antibodies** that inhibited the binding of E2 to CD81 retained the ability to recognize preformed CD81-E2 complexes generated with some of the same recombinant E2 proteins. Two **antibodies** that did not recognize preformed complexes of HCV 1a E2 and CD81 also inhibited binding of HCV 1a virions to CD81. Thus, HCV-infected individuals can produce **antibodies** that recognize conserved conformational epitopes and inhibit the binding of HCV to CD81. The inhibition is mediated via **antibody** binding to epitopes outside of the CD81 binding site in E2, possibly by preventing conformational changes in E2 that are required for CD81 binding.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS

FORMAT

RECORD. ALL CITATIONS AVAILABLE IN THE RE

L5 ANSWER 10 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:167132 CAPLUS

DOCUMENT NUMBER: 134:324893

TITLE: Characterization of hepatitis C virus core-specific immune responses primed in rhesus macaques by a nonclassical ISCOM vaccine

AUTHOR(S): Polakos, Noelle K.; Drane, Debbie; Cox, John; Ng, Philip; Selby, Mark J.; Chien, David; O'Hagan, Derek T.; Houghton, Michael; Paliard, Xavier

CORPORATE SOURCE: Chiron Corp., Emeryville, CA, 94608, USA

SOURCE: Journal of Immunology (2001), 166(5), 3589-3598

CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

TI Characterization of hepatitis C virus core-specific immune responses primed in rhesus macaques by a nonclassical ISCOM vaccine

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AB Current therapies for the treatment of hepatitis C virus (HCV) infection are only effective in a restricted no. of patients. Cellular immune responses, particularly those mediated by CD8+ CTLs, are thought to play

a

role in the control of infection and the response to antiviral therapies. Because the Core protein is the most conserved HCV protein among genotypes, the authors evaluated the ability of a Core prototype vaccine to prime cellular immune responses in rhesus macaques. Since there are serious concerns about using a genetic vaccine encoding for Core, this vaccine was a non-classical ISCOM formulation in which the Core protein was adsorbed onto (not entrapped within) the ISCOMATRIX, resulting in .apprx.1-.mu.m particulates (as opposed to 40 nm for classical ISCOM formulations). The authors report that this Core-ISCOM prototype vaccine primed strong CD4+ and CD8+ T cell responses. Using intracellular staining for cytokines, the authors show that in immunized animals 0.30-0.71 and 0.32-2.21% of the circulating CD8+ and CD4+ T cells, resp., were specific for naturally processed HCV Core peptides. Furthermore, this vaccine elicited a Th0-type response and induced a high titer of Abs against Core and long-lived cellular immune responses. Finally, the authors provide evidence that Core-ISCOM could serve as an adjuvant for the **HCV envelope protein E1E2**. Thus, these data provide evidence that Core-ISCOM is effective at inducing cellular and humoral immune responses in nonhuman primates.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L5 ANSWER 9 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:402645 CAPLUS

DOCUMENT NUMBER: 136:84292

TITLE: Predominance of **antibodies** to hepatitis C  
virus envelope proteins in various disease statuses  
of

hepatitis C

AUTHOR(S): Poduri, C. D.; Khanna, A.; Khundmiri, S. J.; Khaja,  
M.

N.; Kumar, K. S.; Sugunan, V. S.; Habibullah, C. M.;  
Das, M. R.

CORPORATE SOURCE: Rajiv Gandhi Center for Biotechnology, Trivandrum,  
695

014, India

SOURCE: Acta Virologica (English Edition) (2001), 45(1), 1-6

CODEN: AVIRA2; ISSN: 0001-723X

PUBLISHER: Slovak Academic Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

TI Predominance of **antibodies** to hepatitis C virus envelope  
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Sugunan, V. S.; Habibullah, C. M.; Das, M. R.

AB The **antibody** profile to various proteins of hepatitis C virus  
(HCV) was studied in 113 patients pos. for HCV RNA in various disease  
statuses of hepatitis C (HC). A single peptide (E2/NS1, aa 413-436 of

HCV  
polyprotein) chosen from a conserved region at the C-terminus of the  
hypervariable region (HVR) HVR1 of HCV was found to be sufficient for  
reliable diagnosis of the infection, even in the acute phase. Six

hundred  
and one suspected HC cases and 200 voluntary blood donors were tested by  
this peptide. The sensitivity of detection of HCV **antibodies** by  
this peptide did not increase with addn. of peptides from other HCV  
proteins. The authors' results clearly demonstrate that  
**antibodies to HCV envelope proteins**  
occur in a higher percentage of the infected population than those to  
other proteins. This emphasizes the necessity of using representative  
sequences from **HCV envelope proteins** in  
diagnostic immunoassays of this viral infection.

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FORMAT

ER 10 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:167132 CAPLUS

DOCUMENT NUMBER: 134:324893

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AUTHOR(S): Polakos, Noelle K.; Drane, Debbie; Cox, John; Ng, Philip; Selby, Mark J.; Chien, David; O'Hagan, Derek T.; Houghton, Michael; Paliard, Xavier

CORPORATE SOURCE: Chiron Corp., Emeryville, CA, 94608, USA

SOURCE: Journal of Immunology (2001), 166(5), 3589-3598

CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

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CODEN: JOIMA3; ISSN: 0022-1767

AU Polakos, Noelle K.; Drane, Debbie; Cox, John; Ng, Philip; Selby, Mark J.; Chien, David; O'Hagan, Derek T.; Houghton, Michael; Paliard, Xavier

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a role in the control of infection and the response to antiviral therapies. Because the Core protein is the most conserved HCV protein among genotypes, the authors evaluated the ability of a Core prototype vaccine to prime cellular immune responses in rhesus macaques. Since there are serious concerns about using a genetic vaccine encoding for Core, this vaccine was a non-classical ISCOM formulation in which the Core protein was adsorbed onto (not entrapped within) the ISCOMATRIX, resulting in .apprx.1-.mu.m particulates (as opposed to 40 nm for classical ISCOM formulations). The authors report that this Core-ISCOM prototype vaccine primed strong CD4+ and CD8+ T cell responses. Using intracellular staining for cytokines, the authors show that in immunized animals 0.30-0.71 and 0.32-2.21% of the circulating CD8+ and CD4+ T cells, resp., were specific for naturally processed HCV Core peptides. Furthermore, this vaccine elicited a Th0-type response and induced a high titer of Abs against Core and long-lived cellular immune responses. Finally, the authors provide evidence that Core-ISCOM could serve as an adjuvant for the HCV envelope protein E1E2. Thus, these data provide evidence that Core-ISCOM is effective at inducing cellular and humoral immune responses in nonhuman primates.

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RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

ER 9 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:402645 CAPLUS

DOCUMENT NUMBER: 136:84292

TITLE: Predominance of **antibodies** to hepatitis C  
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of

hepatitis C

AUTHOR(S): Poduri, C. D.; Khanna, A.; Khundmiri, S. J.; Khaja,  
M.

N.; Kumar, K. S.; Sugunan, V. S.; Habibullah, C. M.;  
Das, M. R.

CORPORATE SOURCE: Rajiv Gandhi Center for Biotechnology, Trivandrum,  
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PUBLISHER: Slovak Academic Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

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Sugunan, V. S.; Habibullah, C. M.; Das, M. R.

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statuses of hepatitis C (HC). A single peptide (E2/NS1, aa 413-436 of

HCV

polyprotein) chosen from a conserved region at the C-terminus of the  
hypervariable region (HVR) HVR1 of HCV was found to be sufficient for  
reliable diagnosis of the infection, even in the acute phase. Six

hundred

and one suspected HC cases and 200 voluntary blood donors were tested by  
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proteins. The authors' results clearly demonstrate that  
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occur in a higher percentage of the infected population than those to  
other proteins. This emphasizes the necessity of using representative  
sequences from **HCV envelope proteins** in  
diagnostic immunoassays of this viral infection.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR  
THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

ER 6 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:912910 CAPLUS

DOCUMENT NUMBER: 137:104371

TITLE: Secretory expression of different C-terminal truncated

AUTHOR(S): HCV E1 proteins in mammalian cells and characterization of the expressed products  
Zhu, Jun; Kong, Yuying; Liu, Jing; Zhang, Zuchuan; Wang, Yuan; Li, Guangdi  
CORPORATE SOURCE: Institute of Biochemistry and Cell Biology, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China  
SOURCE: Shengwu Huaxue Yu Shengwu Wuli Xuebao (2001), 33(6), 634-640  
CODEN: SHWPAU; ISSN: 0582-9879  
PUBLISHER: Shanghai Kexue Jishu Chubanshe  
DOCUMENT TYPE: Journal  
LANGUAGE: Chinese

TI Secretory expression of different C-terminal truncated HCV E1 proteins in mammalian cells and characterization of the expressed products

SO Shengwu Huaxue Yu Shengwu Wuli Xuebao (2001), 33(6), 634-640

CODEN: SHWPAU; ISSN: 0582-9879

AU Zhu, Jun; Kong, Yuying; Liu, Jing; Zhang, Zuchuan; Wang, Yuan; Li, Guangdi

AB Three fragments of HCV envelope 1 (E1) with different C-terminal truncation at aa310, aa325, aa340 were cloned into the mammalian expression vector pSecTagB. An epitope in the hepatitis B surface antigen, preS1(21-47), were genetically engineered onto the N-terminus of the recombinant protein and used as an affinity tag for detection and purifn. The resulting pSec-preS1-E1t310, pSec-preS1-E1t325, and pSec-preS1-E1t340 were transiently expressed in the HeLa cells and antigenicity, secretory efficiency, and glycosylation type of the recombinant E1 proteins were compared. All of the three recombinant proteins could be detected by both preS1 monoclonal **antibody** and E1 polyclonal antiserum. The expression products were secreted and highly

mannose-type glycosylated, with S1E1t325 being secreted, indicating the influence of the hydrophobic regions on the secretion of the E1 protein. Three CHO cell lines expressing the proteins, S1E1t310, S1E1t325, and S1E1t340, were established and CHO/pSecS1E1t325 was chosen for further study. The secreted S1E1t325 could be enriched from cell culture medium by the preS1 **antibody**-coupled Sepharose. The glycosylation anal. indicated the lack of complex glycogen even after the E1 was secreted via Golgi complexes. The established stable cell lines and anti-preS1 affinity method could be utilized to enrich and purify the HCV E1 expressed in mammalian cells, and may be used for further characterization of this protein.

L5 ANSWER 7 OF 44 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:563383 CAPLUS

DOCUMENT NUMBER: 135:286641

TITLE: Characterization of Pseudotype VSV Possessing HCV Envelope Proteins

AUTHOR(S): Matsuura, Yoshiharu; Tani, Hideki; Suzuki, Kensuke; Kimura-Someya, Tomomi; Suzuki, Ryosuke; Aizaki, Hideki; Ishii, Koji; Moriishi, Kohji; Robison, Clinton

CORPORATE SOURCE: S.; Whitt, Michael A.; Miyamura, Tatsuo  
Research Center for Emerging Infectious Diseases,  
Research Institute for Microbial Diseases, Osaka

SOURCE: University, Osaka, Japan  
Virology (2001), 286(2), 263-275  
CODEN: VIRLAX; ISSN: 0042-6822  
PUBLISHER: Academic Press  
DOCUMENT TYPE: Journal  
LANGUAGE: English

TI Characterization of Pseudotype VSV Possessing HCV  
Envelope Proteins

SO Virology (2001), 286(2), 263-275  
CODEN: VIRLAX; ISSN: 0042-6822

AU Matsuura, Yoshiharu; Tani, Hideki; Suzuki, Kensuke; Kimura-Someya,  
Tomomi;

Suzuki, Ryosuke; Aizaki, Hideki; Ishii, Koji; Moriishi, Kohji; Robison,  
Clinton S.; Whitt, Michael A.; Miyamura, Tatsuo

AB The genome of hepatitis C virus (HCV) encodes two envelope glycoproteins  
(E1 and E2), which are thought to be responsible for receptor binding and  
membrane fusion resulting in virus penetration. To investigate cell  
surface determinants important for HCV infection, we used a recombinant  
vesicular stomatitis virus (VSV) in which the glycoprotein gene was  
replaced with a reporter gene encoding green fluorescent protein (GFP)

and

produced HCV-VSV pseudotypes possessing chimeric HCV E1 or E2  
glycoproteins, either individually or together. The infectivity of the  
pseudotypes was detd. by quantifying the no. of cells expressing the GFP  
reporter gene. Pseudotypes that contained both of the chimeric E1 and E2  
proteins exhibited 10-20 times higher infectivity on HepG2 cells than the  
viruses possessing either of the glycoproteins individually. These  
results indicated that both E1 and E2 envelope proteins are required for  
maximal infection by HCV. The infectivity of the pseudotype virus was

not

neutralized by anti-VSV polyclonal **antibodies**. Bovine  
lactoferrin specifically inhibited the infection of the pseudotype virus.  
Treatment of HepG2 cells with Pronase, heparinase, and heparitinase but  
not with phospholipase C and sodium periodate reduced the infectivity.  
Therefore, cell surface proteins and some glycosaminoglycans play an  
important role in binding or entry of HCV into susceptible cells. The  
pseudotype VSV possessing the chimeric HCV glycoproteins might offer an  
efficient tool for future research on cellular receptors for HCV and for  
the development of prophylactics and therapeutics for hepatitis C. (c)  
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L5 ANSWER 8 OF 44 CAPLUS COPYRIGHT 2003 ACS

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TITLE: Fluorescence correlation spectroscopy as a method for  
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TI Fluorescence correlation spectroscopy as a method for assessment of interactions between phage displaying **antibodies** and soluble antigen

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AU Lagerkvist, Ann Catrin; Foldes-Papp, Zeno; Persson, Mats A. A.; Rigler, Rudolf

AB Phage display is widely used for expression of combinatorial libraries, not least for protein engineering purposes. Precise selection at the single mol. level will provide an improved tool for generating proteins with complex and distinct properties from large mol. libraries. To establish such an improved selection system, the authors here report the detection of specific interactions between phage with displayed **antibody** fragments and fluorescently labeled sol. antigen based on Fluorescence Correlation Spectroscopy (FCS). Our novel strategy

comprises

the use of two sep. fluorochromes for detection of the phage-antigen complex, either with labeled anti-phage **antibody** or using a labeled antigen. As a model system, the authors studied a human monoclonal **antibody** to the hepatitis-C virus (HCV) **envelope protein** E2 and its cognate antigen (rE2 or rE1/E2). The authors could thus assess the specific interactions and

det.

the fraction of specific vs. background phage (26% specific phage). Aggregation of these particular antigens made it difficult to reliably utilize the full potential of cross-correlation studies using the two labels simultaneously. However, with true monomeric proteins, this will certainly be possible, offering a great advantage in a safer and highly specific detection system.

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FORMAT

```

6117 "HCV"
      15 "HCVS"
      6120 "HCV"
            ("HCV" OR "HCVS")
      43287 "ENVELOPE"
      8090 "ENVELOPES"
      48016 "ENVELOPE"
            ("ENVELOPE" OR "ENVELOPES")
      1478859 "PROTEIN"
      991006 "PROTEINS"
      1708848 "PROTEIN"
            ("PROTEIN" OR "PROTEINS")
L4      68 "HCV ENVELOPE PROTEIN"
            ("HCV" (W) "ENVELOPE" (W) "PROTEIN")

=> L1 and L4
L5      44 L1 AND L4

```